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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/960,477	09/24/2001	Yuji Ishihara	2001-1276	6807

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/960,477	ISHIHARA ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-17 and 20-35* is/are pending in the application.

4a) Of the above claim(s) *14-16,19,21-25 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-13,17,20,26-30 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-8-05 has been entered.

Claims 2-4, 18 and 36 have been cancelled.

Claims 1, 5-17, 20-35 are pending.

Claims 14-16, 19, 21-25 and 31-34 have been withdrawn.

Claims 1, 5-13, 17, 20, 26-29, 30 and 35 are considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

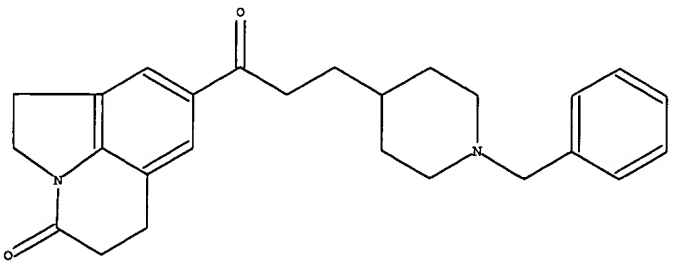
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 1, 5-13, 20, 26-30 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Goto et. al.** (US 5,527,800) and further in view of the teachings of Tobin et. al. and Lai et. al.

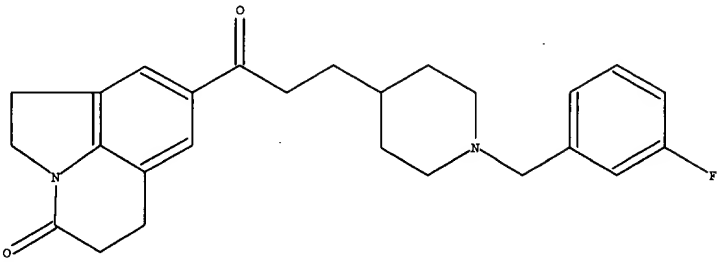
Table 63, lists compounds #38-40 (on columns 207-208) that read on the instantly claimed formula with the following substituents:

- Ar is a peri-fused cycle of (ring C'-N- ring D'-ring A);
- n = 2; R is hydrogen;
- Y is an optionally substituted amino or an optionally substituted nitrogen-containing saturated heterocyclic group;

Note, compound #38 is actually the second compound recited in instant claim 13, which has the following structure:



Likewise, compound #40 is actually the first compound recited in the instant claim 13, which has the following structure:



Goto's compounds can also inhibit acetylcholinesterase. However, Goto's teaching differs from the instantly claimed method by using said compounds to treat senile dementia, Alzheimer's disease, and not to improve "*excretory potency of an urinary bladder*". Such a difference can be overcome by the teachings of Tobin et. al. and Lai et. al.

Tobin et. al. identify three acetylcholine (or muscarinic) receptors: M_1, M_2, and M_3 that affect a bladder. Lai et. al. further reveal that: "*activation of M_2 receptor indirectly contributes to bladder contraction...*" Therefore, from the relationship of muscarinic receptors with urinary bladder taught by Tobin et. al. and Lai et. al., the skilled medicinal chemist would have been motivated to treat a bladder related disorder by improving excretory potency with cholinesterase inhibitors such as those of Goto et. al.

Claims 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goto et. al. (US 5,527,800). Claims 26-28 are drawn to crystal of 8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof. Claim 29 is drawn to the pharmaceutical composition of said crystals. Claim 30 is drawn to an

acetylcholinesterase inhibitor comprising the pharmaceutical composition of claim 29. The teaching of Goto et. al. disclose a closely analogous crystalline compound (see compound #40). Said compound also inhibits acetylcholinesterase. Therefore, it would have been obvious for one skilled in the art to make the claimed crystal and incorporate it in a pharmaceutical composition.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Enablement:** Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 17 recites: "A pharmaceutical composition for improving excretory potency of the urinary bladder which comprises a combination of an α-blocker and a non-carbamate amine compound having an acetylcholinesterase-inhibiting action." The scope of claim 17 covers the combination of any known α-blockers and acetylcholinesterase inhibitors at any proportions. Furthermore, said claim does not seem to limit the number of agents in a particular combination. Thus, the scope of claim 17 is unduly broad.

The amount of direction or guidance presented:

The specification only lists α-blockers that can be combined with non-carbamate acetylcholinesterase inhibitors, but it does not describe how these agents can be mixed and/or administered. Since both α-blockers and acetylcholinesterase inhibitors can affect the heart as well as blood pressure, naming the compounds alone does not sufficiently guide the skilled clinician in combining said agents.

The state of the prior art:

Although an α-blocker such as Terazosin is known to treat BPH, its effect of lowering blood pressure cannot be ignored in a combination with another agent. Most acetylcholinesterase inhibitors are known to cause arrhythmia, or tachycardia, and hypotension. So, the combination of an α-blocker with an acetylcholinesterase inhibitor could potentiate

hypotension or syncope which could cause injury from falling. Furthermore, not every α-blocker is useful for improving excretory potency as evident by the teaching of **Hisayama et. al.**, disclosing α-blockers such as: bunazosin and yohimbine, which do not cause bladder contraction. Therefore, the skilled clinician cannot rely on the state of the prior art to make a composition by combining an α-blocker and an acetylcholinesterase inhibitor.

The relative skill of those in the art:

Even with the advanced training, the skilled clinician would have to engage in undue experimentation to establish data that would adequately support a pharmaceutical composition comprising an α-blocker with an acetylcholinesterase inhibitor. Such a task would require a tremendous amount of effort, time and resources.

The predictability or unpredictability of the art & The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification only lists α-blockers that can be combined with acetylcholinesterase inhibitors without disclosing proportion and/or frequency. However, the possible drug-drug interaction, or the potentiation of adverse effects would place patients in high risk. Thus, with such a limited teaching, the skilled clinician would have to carry out undue experimentation to make a pharmaceutical composition as recited in claim 17.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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7-8-05

Tamthom N. Truong
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